PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

CODE	DATE	NTD

ANKOM 27 JUN 2005 GIPS

DATA ENTERED

FINAL CHECK

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/005400	24.12.2004	05.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D409/12, C07D453/02, C07D333/38, C07D409/14, C07D413/12, C07D413/14, C07D417/14, A61K31/41,

Applicant
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Fritz, M

Telephone No. +49 89 2399-2792

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005400

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005400

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14-23,29

because:

☒ the said international application, or the said claims Nos. 14-23,29 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/005400

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-23,25-36
	No:	Claims	1-3,24
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-13,24-28,30-36
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15-23,29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re Item IV
Lack of unity of invention

The separate inventions are:

Claims 1-7(part);8; 9-10 (part);11;12-31(part); 32-36	Compounds (I) in which Y is CH, methods, compositions, and uses thereof, processes for their poduction, intermediates (XV),(XVI),(XI) and use of these intermediates
1-7(part);9-10(part);12-31(part)	Compounds (I) in which Y is nitrogen, methods, compositions and uses thereof

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

Unity of invention requires a special techical feature which is a contribution to the art. This requirement is not fulfilled, as e.g. several of the substances disclosed in D1 (ex. 20-22, 27) are representatives of the compounds (I) according to the present case and furthermore also known as CHK 1 inhibitors.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 03/028731 A (SMITHKLINE BEECHAM CORPORATION; PARRISH, CYNTHIA, A; CALLAHAN, JAMES,) 10 April 2003 (2003-04-10)
D2: WO 03/029241 A (SMITHKLINE BEECHAM CORPORATION; PARRISH, CYNTHIA, A; CALLAHAN, JAMES,) 10 April 2003 (2003-04-10)
D3: ROBBA M ET AL: "Synthèse d'intermédiaires de la thiazolo [4,5-d] pyridazine. II. Amides et hydrazides d'acides thiazole-carboxyliques" BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE, SOCIETE FRANCAISE DE CHIMIE. PARIS, FR, no. 6, 1969, pages 2152-2157, XP002234183 ISSN: 0037-8968
D4: CHILDRESS ET AL.: "Thiazolopyrimidines" J. AM. CHEM. SOC., vol. 73, no. 26, 1951, pages 3862-3864, XP002330773
D5: CHAUVIN ET AL.: "Synthesis of heterocyclic compounds from cyano- and dicyanoselephenes" COMPTES RENDUS DES SEANCES DE DES SCIENCES, SERIE C: SCIENCES CHIMIQUES, vol. 274, no. 14, 1972, pages 1347-1349, XP009048300

The present application discloses compounds of the general formula (I) (claims 1-11), the compounds (I) for use in therapy (claims 12-14), methods of treatment by administering the compounds (I) (claims 15-23, 29), pharmaceutical compositions thereof (claim 24), the usage thereof for the preparation of a medicament (claims 25-28, 30-31), processes for the preparation thereof (claims 32-34), intermediates of formulas (XV), (XVI) and (XI) (claim 35) as well as the use of these intermediates in the manufacture of a compound (I) (claim 36).

Inventions 1,2

For the assessment of the present claims 15-23, 29 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Present claims 1-10,12-14,24-28,30-34 relate to an extremely large number of possible products. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

The search has therefore been restricted on those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds (I) in which X designates a sulphur atom.

Consequently the following comments with regard to claims 1-10,12-34,36 only refer to the subject-matter thereof which was actually searched (Article 17(2) PCT).

Novelty

Invention 1

Compounds which are structurally extremely close as well as substances which are representatives of the compounds (I) according to the present case (but excluded from the subject-matter of the claims by provisos) are known from D1-D2 (cf. examples therein). The compounds disclosed in these documents are, as the compounds (I) according to the present case, described as being CHK 1 inhibitors and as such useful in the treatment of proliferative diseases.

The intermediate compounds of formulas (XV), (XVI) and (XI) are not known in the art.

The subject-matter of claims 1-36 according to the present case is novel in the sense of Article 33(2) PCT.

Invention 2

Representatives of the compounds (I) in which Y designates N are known in the art:

D3 - compounds 2 in which R = Et or 2-furanyl (p. 2155, right col., 2nd, 3rd cpd.)
D4 - the compounds 2-methylthiazole-4,5-dicarboxamide and 2-phenylthiazole-4,5-dicarboxamide (p. 3863, left col.)

D5 - two compounds represented by the second structural formula of the first reaction equation displayed in the lower part of p. 1348 of D5

The disclosure of D3-D5 is detrimental for the novelty of the subject-matter of claims 1-3 and 24 according to the present case (Article 33(2) PCT).

Inventive step

Invention 1

Closest prior art is any one of D1 and D2.

The problem of the present application was to provide further compounds that are suitable as CHK 1 inhibitors.

There are no pharmacological data in the description showing that this problem has actually been solved, the compounds (I) are - however - an obvious solution to the problem, as they are only novel because of the provisos excluding concrete substances known from D1 and D2 having the same activity.

An inventive step in the sense of Article 33(3) PCT can thus not be acknowledged for the subject-matter of claims 1-34, unless an unexpected effect (as indicated in the description on p. 2, lines 4-5) can be demonstrated which serves to dsitinguish the compounds (I) further from the compounds disclosed in D1 and D2.

The following is stated with regard to the claims comprising the intermediates:

In the case of an intermediate taking part in an analogy process (which is the case here) of a patentable subsequent product, in order to be inventive, this intermediate should make
i) a structural contribution to the subsequent product and
ii) the structural contribution to the subsequent product and the structural contribution provided by the intermediate should display at least one of those features that differentiate the subsequent product from known compounds in the prior art.

The condition ii) is not fulfilled, as representatives of the compounds (I) are already

known from D1 (cf. ex. ex. 20-22, 27) and thus a differentiating technical feature does not exist.

An inventive step in the sense of Article 33(3) PCT is - by consequence - not acknowledged for the subject-matter of claims 35-36.

Invention 2

Closest prior art is any one of D1 and D2.

The problem of the present application was to provide further compounds that are suitable as CHK 1 inhibitors.

There are no pharmacological data in the description showing that this problem has actually been solved; if this were shown, an inventive step in the sense of Article 33(3) PCT could be acknowledged for those compounds (I) which are novel, as they are isosteric analogs of known compounds having a special pharmacological activity, and it can neither be predicted whether an isosteric exchange leaves the pharmacological activities of the starting materials intact nor is such an isosteric modification suggested in D1 and D2.